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Title: A Phase I study investigating the safety and pharmacokinetics of highly bioavailable curcumin (Theracurmin®) in cancer patients

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Conflicts of interest: A. Imaizumi is a consultant to Theravalues Corporation, and Y. Otsuka is an employee of Theravalues Corporation.

Abstract

Background: A growing number of preclinical studies have demonstrated that curcumin could be a promising anticancer drug; however, poor bioavailability has been the major obstacle for its clinical application. To overcome this problem, we developed a new form of curcumin (Theracurmin®) and reported high plasma curcumin levels could be safely achieved after a single administration of Theracurmin® in healthy volunteers. In this study, we aimed to evaluate the safety of repetitive administration of Theracurmin® in cancer patients.

Methods: Pancreatic or biliary tract cancer patients who failed standard chemotherapy were eligible for this study. Based on our previous pharmacokinetic study, we selected Theracurmin® containing 200 mg of curcumin (Level 1) as a starting dose, and the dose was safely escalated to Level 2, which contained 400 mg of curcumin. Theracurmin® was orally administered every day with standard gemcitabine-based chemotherapy. In addition to safety and pharmacokinetics data, NF-κB activity, cytokine levels, efficacy and quality of life (QOL) score were evaluated.

Results: Ten patients were assigned to level 1 and six were to level 2. Peak plasma curcumin levels (median) after Theracurmin® administration were 324 ng/mL (range, 47–1,029 ng/mL) at Level 1 and 440 ng/mL (range, 179–1,380 ng/mL) at Level 2. No

unexpected adverse events were observed and 3 patients safely continued Theracurmin® administration for > 9 months.

Conclusions: Repetitive systemic exposure to high concentrations of curcumin achieved by Theracurmin® did not increase the incidence of adverse events in cancer patients receiving gemcitabine-based chemotherapy.

Introduction

Curcumin is a natural polyphenol derived from turmeric (*Curcuma longa*). In addition to its use as food, coloring agent, and traditional medicine, growing evidence suggests that curcumin could be a promising anticancer drug [8, 39]. In preclinical studies, curcumin exhibits anticancer effects by modulating a variety of molecules involved in cancer progression [2, 23, 24, 26, 41]. Curcumin can also potentiate anticancer effects of cytotoxic agents [2, 11, 23]. For example, Kunnumakkara et al. demonstrated that combination of curcumin with gemcitabine suppressed tumor growth more effectively than curcumin or gemcitabine alone using an orthotopic model of pancreatic cancer [23]. Based on these promising preclinical data, several investigators, including ourselves, have tested this agent in clinical trials [6, 10, 21, 37]. Some clinical benefits were reported; however, plasma curcumin levels remained low, despite taking gram doses of curcumin. Administration of more than 8 g of curcumin failed to increase plasma curcumin levels in a dose-dependent manner in healthy volunteers [42]. Thus, poor bioavailability has been a challenging problem for the clinical application of curcumin. To overcome this problem, many attempts are being made including the application of innovative drug delivery system (liposome, nanoparticle, phospholipids, etc.) or the development of new curcumin analogues [3, 4, 9, 25, 27, 33, 34, 36]. Among these, a novel form of curcumin (Theracurmin®) was developed using a

microparticle and surface-controlled drug delivery system [33]. Theracurmin® exhibits over 30-fold higher bioavailability than conventional curcumin in rats. In addition, we verified that high plasma curcumin levels can be safely achieved after single administration of Theracurmin® in healthy volunteers [19]. Therefore, Theracurmin® could be a useful tool for investigating the anticancer effects of curcumin in clinical trials. The few toxicities have reported in previous clinical studies; however, this may be attributed to low bioavailability of conventional curcumin and the safety of repetitive systemic exposure to high concentrations of curcumin remains unclear. Therefore, we planned this phase I study to verify the safety of repetitive exposure to high concentrations of curcumin achieved by Theracurmin® in this study. In addition to safety and pharmacokinetics data, we evaluated whether the dose tested in this study could inhibit NF-κB, which is one of the well-known targets of curcumin. Cytokine levels, efficacy and quality of life (QOL) score scaled according to the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC-QLQ-C30) were also investigated.

Patients and methods

Eligibility criteria

Patients with pancreatic or biliary tract cancer, who failed standard chemotherapy and had no other effective treatment option, were eligible if they met the following criteria: histological

or radiological confirmation of cancer; age ≥20 years; Eastern Cooperative Oncology Group performance status of 0–1; adequate bone marrow (neutrophil count ≥1,500/mm^3; platelet count ≥100,000/mm^3), liver [total bilirubin ≤3 mg/dL; aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤150 IU/L], and renal (creatinine ≤1.2 mg/dL) functions; adequate oral intake; and provision of written informed consent. Exclusion criteria were pulmonary fibrosis or interstitial pneumonia; severe heart disease; uncontrollable diabetes mellitus; active infection; pregnancy or lactation; childbearing age in women; severe drug hypersensitivity; mental disorder; and other serious medical conditions. This phase I study was conducted in two institutions in Japan. The protocol was approved by the review board of each institution and registered in the University Hospital Medical Information Network Clinical Trials Registry (ID: 000002950). Patient registration and data management were conducted in an independent data center at Hokkaido Information University. All procedures were performed in accordance with the 1964 Declaration of Helsinki.

Theracurmin®

Theracurmin® was prepared as previously reported [33]. Different from the previous studies, we used Theracurmin® in water solution (100 g drink pack) including 0.03% sucralose, 0.15% citrate acid and 0.1% flavor in this study for the convenience of patients. Each drink

pack contains 2 and 4 g of Theracurmin (200 and 400 mg of curcumin) for Level 1 and 2, respectively, in 100 g water solution.

Treatment

Planned doses comprised Theracurmin® contains 100, 200, and 400 mg of curcumin for Level 0, 1, and 2, respectively. (Theracurmin contains 10 w/w% of curcumin). Level 1 was the initial dose selected on the basis of our previous study [19], which proved the safety of single administration Theracurmin® containing 210 mg of curcumin in healthy volunteers. Daily oral Theracurmin® was added to gemcitabine-based chemotherapy. Fourteen patients received gemcitabine/S-1 combination therapy and two received gemcitabine monotherapy. Standard dose and schedule of gemcitabine/S-1 chemotherapy consisted of intravenous administration of gemcitabine 1000 mg/m^2 on day 1 and 8, and 60-80 mg/m^2 of S-1 orally for 14 consecutive days and repeated every 3 weeks [22]. As for gemcitabine monotherapy, it consisted of intravenous administration of gemcitabine 1000 mg/m^2 on day 1, 8 and 15 every 4 weeks [5]. The same dose and schedule of gemcitabine-based chemotherapy were applied as used before enrollment onto this study. Patients were allowed to take the daily Theracurmin® dose at their own convenience, except when monitoring plasma curcumin levels on defined days. Gemcitabine-based chemotherapy was initiated and repeated on

day 1 if the neutrophil count was ≥1,500/mm^3; platelet count was ≥75,000/mm^3; total bilirubin was <3 mg/dL; AST and ALT were <150 U/L; creatinine was <1.5 mg/dL; stomatitis/diarrhea was ≤Grade 1; skin rash was ≤Grade 2; and fever was absent (<38°C). If patients did not meet the above criteria, gemcitabine-based chemotherapy was delayed by 1 week or more until recovery. During suspension of gemcitabine-based chemotherapy, Theracurmin® administration was also suspended. The dose and schedule of gemcitabine-based chemotherapy was adjusted at the discretion of the treating physician according to the adverse events observed during the previous cycle. Treatment was continued until any of the following occurred: discontinuation of gemcitabine-based chemotherapy because of disease progression-based deterioration of general condition; Theracurmin® intolerance; unacceptable toxicity related to Theracurmin®; >4-week delay of the treatment schedule; or patient refusal.

Definition of dose-limiting toxicities and maximum tolerated dose

Dose-limiting toxicities (DLTs) were determined during the first cycle of concomitant gemcitabine-based chemotherapy and defined as ≥Grade 3 nonhematological toxicity (except abnormal blood tests) or patient refusal because of Theracurmin® intolerance. If only one or two of the six patients experienced DLTs at Level 1—the selected starting

dose—the dose was escalated to Level 2. No escalation in the dose was allowed in individual patients. The maximum tolerated dose (MTD) was defined as that causing DLTs in three or more of the six patients. If the MTD had been reached at Level 1, the dose would have been planned to be decreased to Level 0 (Theracurmin® containing 100 mg).

Pretreatment and follow-up evaluation

Pretreatment evaluation included obtaining patient medical history and performing a physical examination, complete blood cell count, and serum biochemical tests. Physical examinations and blood tests were scheduled on the day of gemcitabine administration. Carcinoembryonic antigen and carbohydrate antigen 19-9 were monitored every month. Toxicity was evaluated using the Common Toxicity Criteria Adverse Events version 4.0. Imaging tests were planned 8 weeks after treatment initiation, and the objective response rate was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 in patients with measurable target lesions. Additional imaging tests were performed if clinically indicated or at the discretion of the treating physician.

Measurement of plasma curcumin levels by high-performance liquid chromatography–mass spectrometry/mass spectrometry

Plasma curcumin levels were monitored at two time points on day 1 of the second treatment cycle (in cases 13 and 16, plasma curcumin levels were monitored on day 1 of the first treatment cycle). The first blood draw was performed just before Theracurmin® administration, representing the nadir. Patients took their daily Theracurmin® dose, and the second blood draw was performed 2 h later, representing the peak, according to our previous study [19]. Plasma curcumin levels were measured by high-performance liquid chromatography-mass spectrometry/mass spectrometry as previously reported [19, 21], and the lower limit of detection was 0.5 ng/mL.

NF-κB activity

When developing new target-based drugs, it is desirable to demonstrate that the target can be inhibited at the dose administered rather than to determine the MTD [15]. NF-κB is one of the well-known targets of curcumin [23, 24, 26] and Dhillon et al. reported NF-κB inhibition in peripheral blood mononuclear cells (PBMCs) after 8 g of conventional curcumin administration using immunocytochemistry. Therefore, we selected NF-κB as the target of Theracurmin® and evaluated the changes of NF-κB activity in PBMCs using immunocytochemistry. To obtain PBMCs, 8 mL of blood was drawn 2 h after gemcitabine administration on day 1 of the first and second cycles. PBMCs were collected using a BD

Vacutainer® Cell Preparation Tube (Becton, Dickinson and Company, Franklin Lakes, NJ, USA) according to the manufacturer's instructions. Collected PBMCs were then analyzed via immunocytochemistry, as previously reported [10]. Anti-human phospho-NF-κB p105 antibody (#4808S; Cell Signaling Technology, Danvers, MA, USA) was chosen.

Cytokine levels

Anti-inflammatory effect is another property of curcumin [38, 39]. Pro-inflammatory cytokines such as interleukin-6 (IL-6) or tumor necrosis factor-α (TNF-α) are reportedly associated with fatigue in cancer patients [28, 35]. Furthermore, curcumin can attenuate the expression of these cytokines in vitro [7]. Therefore, we monitored changes in these cytokine levels in the blood after Theracurmin® administration in seven patients. Blood draws were performed 2 h after gemcitabine administration on day 1 of the first and second cycles. Cytokine levels were measured by commercially available, standard enzyme-linked immunosorbent assays.

QOL assessment

QOL scores were assessed using the EORTC QLQ-C30 version 3.0 [1, 30]. Patients were asked to scale their symptoms on day 1 of each cycle and submit their scoring sheets to an

independent data center. Scores were translated into scales ranging from 0 to 100 according to the EORTC QLQ-C30 manual [14]. Five functional scores (emotional, role, cognitive, physical, and social) were pooled. A higher score indicates a better symptom for functioning and global health status, whereas a lower score indicates a better symptom for other items. QOL scores are presented as means ± standard deviations.

Statistical methods

For statistical analysis, we used the paired Student's *t*-test for QOL scores and the Mann–Whitney *U* test for plasma curcumin and cytokine levels. Bonferroni correction was made for multiple comparisons of QOL scores, and $P < 0.005$ was considered significant. The final analysis was conducted in October 2012. All statistical analyses were performed using SPSS version 14.0J (SPSS Japan Inc., Tokyo, Japan).

Results

Patient characteristics

We enrolled 16 patients between February 2011 and January 2012. Patient characteristics are shown in Table 1. Median age was 64 years (range, 50–84 years). Fourteen patients had pancreatic cancer and two had biliary tract cancer. All patients previously received

gemcitabine and S-1 and had no other effective treatment option at enrollment. Median number of prior chemotherapies was two (range, 1–4). Theracurmin® was added to gemcitabine/S-1 combination therapy in 14 patients and to gemcitabine monotherapy in 2 patients.

DLTs

Detailed information for each patient is summarized in Table 2. Seven patients were assigned to Level 1 (Theracurmin® containing 200 mg of curcumin). DLTs in one patient (case 2) were unassessable following withdrawal because of disease progression-related deterioration in general condition. One patient (case 6) who was taking opioids for abdominal cancer pain reported increased abdominal pain after Theracurmin® administration. We considered this a DLT and discontinued treatment. Another patient (case 3) reported increased abdominal pain during the second treatment cycle. This did not meet the DLT criteria because the complaint developed during the second treatment cycle. Computed tomography (CT) revealed deterioration of peritonitis carcinomatosa to be the likely cause of abdominal pain; however, we consulted with the data and safety monitoring committee and assigned three additional patients to Level 1 to evaluate the association between increased abdominal pain and Theracurmin® administration. None of these

patients reported abdominal pain. Therefore, we escalated the dose to Level 2 (Theracurmin® containing 400 mg of curcumin). Six patients were assigned to Level 2. DLTs in one patient (case 16) were unassessable following withdrawal because of disease progression-related deterioration in general condition. No DLTs were observed in the other patients.

Toxicities

The overall adverse events are summarized in Table 3. Grade 3–4 neutropenia, leucopenia, anemia, and thrombocytopenia were observed in 38%, 38%, 13%, and 0% of Level 1 patients, and 20%, 20%, 40%, and 0% of Level 2 patients, respectively. Excluding two cases of Grade 3 abdominal pain mentioned previously, other Grade 3–4 nonhematological adverse events included Grade 3 infection (n = 1) at Level 1 and Grade 3 elevated alkaline phosphatase (n = 1) at Level 2. Both of these were likely attributable to disease progression. Three patients (cases 1, 8, and 14) continued Theracurmin® administration for >9 months. We observed no unexpected adverse events attributable to long-term Theracurmin® administration in these three patients.

Plasma curcumin levels

We measured plasma curcumin levels in 14 patients. Median plasma curcumin levels immediately before Theracurmin® administration on day 1 of the second treatment cycle (representing the nadir) were 71 ng/mL (range, <5–208 ng/mL) at Level 1 and 129 ng/mL (range, 50–192 ng/mL) at Level 2. Median plasma curcumin levels 2 h after Theracurmin® administration (representing the peak) were 324 ng/mL (range, 47–1,029 ng/mL) at Level 1 and 440 ng/mL (range, 179–1,380 ng/mL) at Level 2 (Figure 1). Therefore, Theracurmin® could safely increase plasma curcumin levels in a dose-dependent manner.

NF-κB activity

NF-κB is one of the well-known targets of curcumin [23, 24, 26]. To determine whether NF-κB activity is inhibited at the dose tested in this study, we evaluated the changes of NF-κB activity in PBMCs using immunocytochemistry as previously reported [10]. Unfortunately, we could not clearly demonstrate significant changes in NF-κB activity after Theracurmin® administration (data not shown).

Cytokines

Anti-inflammatory effect is another property of curcumin [38, 39]. Pro-inflammatory cytokines such as interleukin-6 (IL-6) or tumor necrosis factor-α (TNF-α) are reportedly

associated with fatigue in cancer patients [28, 35]. Furthermore, curcumin can attenuate the expression of these cytokines *in vitro* [7]. Therefore, we monitored changes in these cytokine levels in the blood after Theracurmin® administration in seven patients. Median IL-6 levels in the plasma before and after Theracurmin® administration were 3.4 pg/mL (range, 1.8–10.8 pg/mL), and 4.4 pg/mL (range, 2.0–12.0 pg/mL), respectively. Similarly, median TNF-α levels were 1.1 pg/mL (range, 0.6–2.9 pg/mL), and 1.3 pg/mL (range, 0.8–2.9 pg/mL), respectively. Therefore, no significant change in cytokine levels was observed among the seven evaluated patients.

Efficacy

Of the 12 evaluable patients, none experienced a partial or complete response, and three (25%) demonstrated stable disease according to RECIST. All of the 14 patients with pancreatic cancer died at the time of final analysis. The median survival time (MST) was 132 days (95% confidence interval: 53–210 days) and three patients (21%) survived for >12 months.

QOL scores

Complete EORTC QLQ-C30 scores on day 1 of the first treatment cycle (baseline) and on

day 1 of the second or later treatment cycles were available in 12 patients. Three patients could not submit the score sheet after Theracurmin® administration because of withdrawal or DLTs, and one failed to complete the score sheet. Changes in QOL scores after Theracurmin® administration are summarized in Table 4. Fatigue- and functioning-associated QOL scores significantly improved after Theracurmin® administration, even after adjustment for multiple comparisons (Table 4). The appetite-associated QOL score also improved by 16.7, although this difference was not statistically significant.

Discussion

A growing number of preclinical studies have demonstrated curcumin could be a promising anticancer drug [2, 23, 24, 26, 41]; however, poor bioavailability has been the major obstacle for the clinical application of curcumin. To overcome this problem, Theracurmin® was developed using a microparticle and surface-controlled drug delivery system and demonstrated over 30-fold higher bioavailability than conventional curcumin in rats [33]. Furthermore, we previously reported that high plasma curcumin levels could be safely achieved after a single administration of Theracurmin® in healthy volunteers [19]. The few toxicities have reported in previous clinical studies testing curcumin; however, this may be attributed to low bioavailability of conventional curcumin and the safety of repetitive systemic

exposure to high concentrations of curcumin remains unclear. Therefore, we planned this study to determine whether repetitive Theracurmin® administration could safely increase plasma curcumin levels in cancer patients. Median plasma curcumin levels 2 h after Theracurmin® administration (representing peak levels) were 324 ng/mL (range, 47–1,029 ng/mL) at Level 1 (Theracurmin® containing 200 mg of curcumin) and 440 ng/mL (range, 179–1,380 ng/mL) at Level 2 (Theracurmin® containing 400 mg of curcumin). These values were significantly higher than the median values (85 ng/mL) achieved in our previous study using 8 g of conventional curcumin [21]. Interpatient variability was large and peak plasma curcumin levels did not increase as expected in some patients. This may be partly attributable to delayed gastric emptying caused by surgery for primary cancer [13] or to the primary cancer itself. For example, endoscopic examination revealed pyloric stenosis caused by pancreatic cancer invasion in case 7 and this may have caused the low plasma curcumin levels in this patient. We could monitor plasma curcumin levels after Theracurmin® administration for >6 months in cases 1 and 8. Plasma curcumin levels 0 and 2 h after Theracurmin® administration were 238 and 1,176 ng/mL, respectively, in case 1 (monitored at 9 months) and 260 and 935 ng/mL, respectively, in case 8 (monitored at 7 months). Interestingly, these values were much higher than those observed on day 1 of the second cycle (Table 2), suggesting that Theracurmin® bioavailability cumulatively increases after

repeated administration. Vareed et al. mentioned that repeated daily administration of curcumin may cause its accumulation at the mucosal surface and increase plasma levels [42]. Further studies are necessary to verify this hypothesis.

Regarding safety, two patients reported increased abdominal pain after Theracurmin® administration. CT scan before Theracurmin® administration in these patients revealed dilated colons, which could be attributed to intestinal obstruction caused by peritonitis carcinomatosa. Consistent with our observations, Epelbaum *et al*. also reported abdominal fullness or pain related to curcumin administration in patients with pancreatic cancer [12]. We speculate that curcumin irritates the intestine, potentially increasing abdominal pain in patients with intestinal obstruction due to peritonitis carcinomatosa or other reasons. In future clinical trials, we advise caution in administering curcumin to such patients.

Other toxicities were comparable with those of gemcitabine-based chemotherapy [22] and the repetitive exposure to high concentrations of curcumin did not cause unexpected serious adverse events or increase the incidence of adverse events in patients with pancreatic or biliary tract cancer receiving gemcitabine-based chemotherapy.

Regarding efficacy, no responses were observed in this study according to RECIST; however, the MST was 132 days (95% confidence interval: 53–210 days) for 14 patients with pancreatic cancer and three patients (21%) survived for >12 months. We believe that

these results are promising, considering the poor prognosis of patients with pancreatic cancer who received only best supportive care after progression on gemcitabine [31].

In our previous study [21], some patients reported improved QOL after curcumin administration. In line with our observation, Sharma et al. reported QOL improvement after curcumin administration [37]. Therefore, we prospectively assessed QOL scores using EORTC QLQ-C30, which is widely accepted as a standard tool to evaluate QOL [1, 30]. Consistent with previous observations, fatigue- and functioning-associated QOL scores significantly improved during Theracurmin® administration, even after adjustment for multiple comparisons. In five patients, the fatigue score improved by >20, which is interpreted as a significant and clinically relevant change [30]. Preclinical studies demonstrating the benefit of curcumin on heart failure, depression, and fatigue [17, 29, 43] support our current findings. Since improved QOL has been demonstrated to contribute to a better outcome in cancer patients [40], it is tempting to speculate that Theracurmin® can improve the outcome of cancer patients through an improvement in QOL. A randomized placebo-controlled clinical trial enrolling a larger cohort is warranted to verify this hypothesis.

Most of the orally administered curcumin is metabolized into curcumin glucuronide and curcumin sulfate and only little amount of parent curcumin exist in plasma [18]. Some group claimed that high plasma curcumin levels achieved by Theracurmin® were clinically

irrelevant because these were of curcumin conjugates [16]. We have responded to this comment and shown some reports supporting our data [20]. Vareed et al. has proposed that conjugated curcumin can exert its activity after deconjugation at the target sites [42]. Pfeiffer et al. demonstrated that conjugated curcumin itself holds some important biological functions [32]. Therefore, we believe that high plasma curcumin levels achieved by Theracurmin® can potentially improve the anticancer effects of this agent in cancer patients. When developing new target-based drugs, it is desirable to demonstrate that the target can be inhibited at the dose administered rather than to determine the MTD, which is the conventional endpoint for cytotoxic drugs [15]. NF-κB is one of the well-known targets of curcumin [23, 24, 26] and Dhillon et al. reported NF-κB inhibition in PBMCs after 8 g of conventional curcumin administration using immunocytochemistry [10]. Therefore, we selected NF-κB as the target of Theracurmin® and evaluated the changes of NF-κB activity in PBMCs using immunocytochemistry. In contrast to the report by Dhillon et al., we could not observe the significant change of NF-κB activity in PBMCs. The reasons for this discrepancy between our results and those of Dhillon et al. remain unclear. Because we could achieve higher plasma curcumin levels compared with those reported by Dhillon et al. (maximum concentration ≤125 ng/mL), plasma curcumin level was unlikely to be a major reason. Evaluation of NF-κB activity in tumor tissues is preferable; however, there exist

ethical problems for repeating a tumor biopsy in patients with pancreatic or biliary tract cancer because of its invasiveness. Optimal dose of Theracurmin® to exert anticancer effects remains to be clarified in the future studies.

In summary, repetitive systemic exposure to high concentrations of curcumin achieved by Theracurmin® did not increase the incidence of adverse events in cancer patients receiving gemcitabine-based chemotherapy.

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Tables

Table 1. Patient characteristics

Total no. of patients enrolled	16
No. of patients evaluated for DLT	14
No. of patients evaluated for QOL	12
Gender	
Male	11 (68%)
Female	5 (32%)
Median age (years)	64 (range 50–84)
Tumor type	
Pancreas	14 (87%)
Biliary tract	2 (13%)
Disease status	
Unresectable	7 (44%)
Recurrent	9 (56%)
Prior no. of chemotherapies	
1	3 (19%)
2	11 (69%)
≥3	2 (13%)
Concomitant regimen	
GEM/S-1	14 (87%)
GEM	2 (13%)
Performance status	
0	9 (57%)
1	7 (43%)
Median CEA (ng/mL)	15 (range 2–258)
Median CA19-9 (U/mL)	1,227 (range 1–69,845)

Table 2. Detailed information and plasma curcumin levels in each patient

Case	Level	Age	Gender	Tumor type	PS	Prior no. of chemo	Surgery for primary lesion	Regimen	BSA ($/m^2$)	Plasma curcumin levels (ng/mL)		Response by RECIST
										0 h	2 h	
1	1	56	male	Pancreas	0	1	yes	GEM/S-1	1.60	33	288	SD
2	1	70	male	Pancreas	1	2	yes	GEM/S-1	1.62	88	361	PD
3	1	66	male	Pancreas	1	2	no	GEM/S-1	1.44	NE	NE	NE
4	1	72	male	Pancreas	0	2	yes	GEM/S-1	1.52	8	145	PD
5	1	57	female	Biliary tract	0	3	yes	GEM/S-1	1.67	103	379	PD
6	1	54	male	Pancreas	0	1	no	GEM/S-1	1.57	NE	NE	NE
7	1	72	male	Pancreas	0	4	no	GEM/S-1	1.60	53	47	PD
8	1	59	female	Pancreas	0	2	no	GEM/S-1	1.57	112	406	SD
9	1	82	male	Pancreas	1	2	yes	GEM/S-1	1.47	208	165	NE
10	1	69	male	Pancreas	0	2	yes	GEM	1.62	<5*[1]	1,029	PD
11	2	62	female	Pancreas	1	1	no	GEM/S-1	1.38	89	251	PD
12	2	61	female	Pancreas	1	2	yes	GEM/S-1	1.32	168	498	PD
13	2	84	male	Pancreas	1	2	yes	GEM	1.52	<5*[1, 2]	1,380	PD
14	2	59	male	Pancreas	0	2	no	GEM/S-1	2.06	50	383	SD
15	2	50	female	Biliary tract	0	2	yes	GEM	1.31	192	179	PD
16	2	67	male	Pancreas	1	2	no	GEM	1.65	<5*[1, 2]	536	NE

BSA body surface area *1 Below the lower limit of detection; *2 Plasma curcumin levels were monitored on day 1 of the first cycle

Table 3. Toxicities

	Level 1 (n = 8)		Level 2 (n = 5)	
	Gr 1–2	Gr 3–4	Gr 1–2	Gr 3–4
Neutropenia	2	3	1	1
Leucopenia	3	3	1	1
Anemia	7	1	1	2
Thrombocytopenia	6	0	0	0
Febrile neutropenia	NA	0	NA	0
Anorexia	2	0	2	0
Nausea	1	0	0	0
Vomiting	2	0	0	0
Fatigue	2	0	1	0
Diarrhea	3	0	0	0
Stomatitis	3	0	0	0
Constipation	2	0	2	0
Fever	3	0	1	0
Infections (others)	0	1	0	0
Biliary tract infection	NA	0	NA	0
AST	6	0	2	0
ALT	4	0	2	0
Albumin	8	0	4	0
Hyperbilirubinemia	2	0	0	0
Creatinine	0	0	0	0
Alkaline phosphatase	5	0	2	1

NA not applicable

Table 4. Changes in quality of life scores

	Baseline	Best score during curcumin intake	Mean change	*P* value[*3]
Fatigue score	**38.0 ± 13.2**	**24.8 ± 14.3**	**−13.2**	**0.004**
Functional score*[1,2]	**82.8 ± 11.9**	**90.7 ± 8.1**	**8.0**	**0.001**
Diarrhea	**15.0 ± 27.6**	**5.6 ± 12.4**	**−9.4**	**0.006**
Financial difficulties	**16.7 ± 25.5**	**2.8 ± 9.2**	**−13.9**	**0.027**
Appetite loss	**38.9 ± 26.6**	**22.2 ± 28.3**	**−16.7**	**0.026**
Insomnia	**13.9 ± 16.4**	**8.3 ± 14.4**	**−5.6**	**0.083**
Pain	**22.2 ± 19.6**	**16.7 ± 18.0**	**−5.5**	**0.083**
Nausea	**6.9 ± 10.7**	**2.8 ± 4.2**	**−4.1**	**0.096**
Constipation	**19.4 ± 21.3**	**11.1 ± 20.8**	**−8.3**	**0.214**
Dyspnea	**25.0 ± 27.6**	**16.7 ± 21.5**	**−8.3**	**0.215**
Global health*[2]	**56.3 ± 18.7**	**63.2 ± 20.0**	**6.9**	**0.101**

*1 Five functional scores (emotional, role, cognitive, physical, and social functions) were pooled together

*2 A higher score indicates a better symptom; otherwise, a lower score indicates a better symptom

*3 $P < 0.005$ was regarded as significant for multiple comparisons

Figure 1. Plasma curcumin levels 2 h after Theracurmin® administration. Each point corresponds to an individual patient. The bar denotes the median value.